



Featured Article

A prognostic model of Alzheimer's disease relying on multiple longitudinal measures and time-to-event data

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Abstract

Introduction: Characterizing progression in Alzheimer's disease is critically important for early detection and targeted treatment. The objective was to develop a prognostic model, based on multivariate longitudinal markers, for predicting progression-free survival in patients with mild cognitive impairment.

Methods: The information contained in multiple longitudinal markers was extracted using multivariate functional principal components analysis and used as predictors in the Cox regression models. Cross-validation was used for selecting the best model based on Alzheimer's Disease Neuroimaging Initiative-1. External validation was conducted on Alzheimer's Disease Neuroimaging Initiative-2.

Results: Model comparison yielded a prognostic index computed as the weighted combination of historical information of five neurocognitive longitudinal markers that are routinely collected in observational studies. The comprehensive validity analysis provided solid evidence of the usefulness of the model for predicting Alzheimer's disease progression.

Discussion: The prognostic model was improved by incorporating multiple longitudinal markers. It is useful for monitoring disease and identifying patients for clinical trial recruitment.

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Keywords:

Mild cognitive impairment; Multivariate functional component analysis; Prediction; External validation; ADNI

1. Introduction

The growing public health threat posed by Alzheimer's disease (AD) has raised the urgency to discover and assess prognostic markers for the early detection of the disease. In this regard, a great deal of effort has been dedicated to

building models for predicting AD based on a single marker, or a combination of multiple markers, which captures the heterogeneity among subjects and detects the disease progression of subjects at risk [1].

Because mild cognitive impairment (MCI) is a risk state for AD, existing research has identified a number of biomarkers that predict clinical changes of MCI patients [2–7], including neurocognitive markers, neuroimaging markers, genetics, and cerebrospinal fluid (CSF)-based markers. Although these studies showed an enhancement of the prognostic value when multivariate markers are considered, the prediction was either qualitative change (i.e., conversion from MCI to AD as a binary response) or quantitative change (i.e., cognitive scores) in the next few years. These studies did not examine the prediction of time from MCI to AD, which is usually the primary outcome in prevention clinical studies of AD [8].

The authors have declared that no conflict of interest exists.

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Relatively few recent studies have investigated the timing from MCI to AD over the duration of follow-up based on Cox regression models [9–11]. These studies assessed the predictive utility of various candidate prognostic markers independently or in combination but only focused on the baseline measurements of the markers. Li et al. [12] developed a joint modeling of longitudinal and time-to-event data technique to examine the comparative utility of the longitudinal markers in determining the risk of incident AD conversion at future time points. However, they analyzed each longitudinal marker independently because of the limitation of the current state-of-the-art joint modeling software. To our knowledge, no prior study has leveraged multiple longitudinal markers and time-to-event information jointly to investigate the prognosis of AD.

The overarching goal of this study is to develop a prognostic model, which relies on serial measurements of multiple markers, for predicting progression-free survival in patients with MCI. The prognostic model uses several cutting-edge statistical methods, which enable it to facilitate clinical decision making based on all the information collected. We evaluated the model using data from the Alzheimer's Disease Neuroimaging Initiative 1 (ADNI-1), a public data set that is well suitable for this task because of its large sample size, breadth of markers, and prospective structure. The combined prognostic value of longitudinal neurocognitive tests, neuroimaging, genetics, and CSF markers was assessed using the prognostic model. External validation of the model is carried out on ADNI-2 to demonstrate the usefulness of the model across studies. The main output of the prognostic model is a prognostic index which can be updated over time as new measurements are available. Such an index is useful for monitoring disease progression for MCI patients and to enrich clinical trials with subjects likely to develop AD in the time frame of the trial.

2. Materials and methods

2.1. Study population

ADNI is a longitudinal observational study investigating whether serial brain imaging, clinical, and neuropsychological assessments can be combined to measure the progression of AD. Detailed information regarding the ADNI study's procedures, including participant inclusion and exclusion criteria, and the complete study protocol can be found at <http://www.adni-info.org/>. The ADNI-1 data set included 379 patients with amnesic MCI at baseline evaluation who had at least one follow-up visit. Criteria for MCI diagnosis were the same as defined by Petersen et al. [13]. As part of the ADNI-1, subjects were assessed at baseline, 6, 12, 18, 24, and 36 months, and continued follow-ups were conducted annually as part of the ADNI-2. The ADNI-2 study had the same overall goals as ADNI-1. ADNI-2 enrolled

an additional group of 424 patients in early MCI, late MCI, and significant memory concern, with at least one follow-up visit and collected over 4-year worth of longitudinal data. We considered all these subjects as MCI patients in our analysis. All subjects were given a written informed consent at the time of enrollment, and the study has been approved by the local institutional review board at all participating sites. The data are publically available at <http://ida.loni.ucla.edu/> and were downloaded on April 15, 2017.

In the present study, the candidate prognostic factors were the longitudinal neurocognitive and imaging markers with the strongest predictive utility identified by Li et al. [12] and are available in both ADNI-1 and ADNI-2 data sets: Alzheimer Disease Assessment Scale–Cognitive 13 items (ADAS-Cog 13); Rey Auditory Verbal Learning Test (RAVLT immediate: sum of five trials; RAVLT learning: trial 5–trial 1); Functional Assessment Questionnaire; Mini–Mental State Examination; volumetric data of middle temporal gyrus (MidTemp) and hippocampus from structural magnetic resonance imaging; and fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET). We also considered CSF biomarkers, total tau, and amyloid β 1–42 peptide, which have been identified as being among the most promising and informative AD biomarkers [14,15]. Relevant demographic and genetic variables (i.e., age, gender, education, and *APOE* ϵ 4 genotype) were used as other prognostic variables given their potential effects on disease progression in AD [16]. Sample size and descriptive statistics for key variables at baseline are shown in Table 1.

2.2. Statistical analysis

We adopted a novel method to jointly model the historical observations of markers as well as time-to-event of interest (e.g., conversion from MCI diagnosis to AD diagnosis) using a functional principal component (FPC) approach and Cox regression model [17,18]. The observed longitudinal values of a specific marker were assumed to come from a latent longitudinal process. The FPC analysis was used to extract the trajectory pattern of the process [19]. The overall trend and changing patterns of the marker were estimated from the entire sample. Each marker trajectory of an individual was summarized as a set of FPC scores. This approach has the advantage of handling missed, irregularly observed data, measurement errors, and no prespecified form of the longitudinal trajectory [19]. Because the longitudinal markers of interest were all associated with AD and are likely to be highly correlated, a nonnegligible correlation may exist between the FPC scores that were derived individually from each longitudinal marker. The correlated scores can lead to interpretation difficulty and multicollinearity issues in the regression analysis. To address this issue, we adopted a multivariate FPC (MFPC) approach [20], which extends the FPC approach by accounting for the correlation among multiple longitudinal markers. We used the MFPC

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